REMARKS

Claims 1-3, 7-17, 25-42 and 44-45 were pending. Applicants have amended claim 45 to correct the antecedent basis. No new matter is added. Claims 1-3, 7-17, 25-42 and 44-45 are pending and under consideration.

35 U.S.C. § 103(a) – Obviousness

Claims 1-3, 7-17, 25-42 and 44-45 are rejected under 35 U.S.C. § 103(a) as obvious over Bennett et al. (US 6,096,722) in view of Yacyshyn (Current Opinion 1999), Sandborn (US 5846983), Kono (US 6730702), Karp (Digestive Disease and Sciences 1988), Sachetto (US 7341741), Yachyshyn (Alimentary Pharm. & Ther. 2002), Patel (Europ. J. Gastroenter. & Hepatology 1995), Svaninger (Scandinavian J. Gastroent. 1993), and Sandborn (Trends in Inflamm. Bowel Dis. 1996). The Examiner concludes that it would have been obvious to use "the claimed IBD treatment methods of Bennett et al. to reduce pouchitis symptoms by reducing PDAI scores." *Office Action* at 7 (emphasis in original). The Examiner states that there was a reasonable expectation of success in treating pouchitis because the art teaches that "one can interchangeably use UC/CD treatment methods to treat pouchitis" (Sandborn; Kono; Sachetto). *Id.* at 8. The Examiner also asserts that there was a reasonable expectation of success based on the reports of tolerability, tissue uptake and bioavailability for enema formulations of ISIS 2302 reported in Yacyshyn (1999), and Bennett (Examples 47-48 and 55), and that dosing and use of enemas was routine in the art (Yacyshyn 2002; Karp; Sandborn; Kono; Sachetto). *Id.* at 8-9.

In addition, the Examiner states that remission of pouchitis and the results disclosed in Example 17 were "reasonably expected" in view of the results obtained by using intravenously administered ISIS 2302 to treat Crohn's disease (Yacyshyn 1999 and 2002; Bennett), as well as the use of non-antisense drugs administered by anal injection or enemas to treat pouchitis (Kono; Karp). *Id.* at 9-10. Applicants respectfully traverse.

Lack of a prima facie *case of obviousness*

The pending claims are directed to a method of treating pouchitis in a human by rectally administering a pharmaceutical composition comprising an antisense oligonucleotide having the nucleobase sequence recited in SEQ ID NO: 1. To establish that this method is *prima faice*

obvious, it is the Office's burden to demonstrate that the cited references provide a reasonable expectation of success, or that the results are predictable – Applicants do not have to establish a lack of an expectation of success or unpredictability. *See M.P.E.P. §2143.* Applicants submit that the Office has failed to establish a *prima facie* case of obviousness for at least the reason that it has failed to meet its burden of establishing that there is a likelihood of success or predictable results.

This is also the conclusion of Dr. Yacyshyn, the lead author of two of the references relied on by the Examiner.

Applicants submit herewith the Declaration of Dr. Bruce Yacyshyn ("Declaration"), an expert who has extensive experience in the field of IBDs as both a clinician and research scientist. *Declaration* at ¶¶ 1-2. Dr. Yacyshyn has reviewed the current Office Action and cited references, and it is his expert opinion that at the time of the invention, there was no reasonable expectation of success. *Id.* at ¶ 8.

Dr. Yacyshyn's opinion is based in part on the fact that, while CD, UC and pouchitis are all disease characterized by inflammation of the bowel, they are distinct diseases and treatments are not interchangeable. He confirms that standard treatment for pouchitis was, and continues to be, antibiotics and probiotics. *Id.* at ¶ 6. This is in contrast to standard treatments for CD and UC, which involves primarily anti-inflammatories and immuno-suppressants. *Id.* at ¶¶ 6 and 7. It is his expert opinion that based on what was known in the art at the time of the invention, the understanding of those of skill in the art was that "there was no reasonable expectation that what was successful in treating CD or UC would be successful in treating pouchitis. This understanding applied to treatments generally, as well as to the claimed method of treating pouchitis with an enema containing ISIS 2302, specifically." *Id.* at ¶ 8 (emphasis added).

Dr. Yacyshyn states that the three references cited by the Examiner which allegedly disclose treatments which were applicable to CD, UC and pouchitis do not support the Examiner's conclusion that one can treat pouchitis with the same methods used to treat CD or UC. *Id.* at ¶ 9. He notes that Sandborn does not contain any data to support the assertion that nicotine can treat all three diseases, and therefore "constitutes nothing more than educated speculation..." *Id.* at 10. Dr. Yacyshyn also notes that Sachetto only discloses a single working example – treating pouchitis – and concludes that this reference's assertion that the disclosed

enemas can treat all three diseases is "speculation which is not supported by sufficient evidence." *Id.* Finally, although Kono discloses anecdotal evidence of treating one CD patient, one pouchitis patient, and three UC patients with an anti-ulcer drug, Dr. Yacyshyn states that "this limited evidence is not sufficient to establish a general expectation that a compound which successfully treats CD, UC or both will also successfully treat pouchitis. Nor is it sufficient to reasonably establish the specific expectation that an enema comprising ISIS 2302 could successfully treated pouchitis, as ecabet sodium is not an antisense compound and is not known to regulate ICAM-1 levels." *Id.* He concludes by stating that "[i]t is my opinion that the references relied on by the Examiner, alone or in combination, are not sufficient to overcome [the] general understanding..." that a treatment which was successful at treating CD, UC or both would not reasonably be expected to also successfully treat pouchitis. *Id.* (emphasis added).

It important to note none of the three references above disclose antisense treatments, and there is nothing in the record which suggests that any of these treatments inhibit ICAM-1. Thus, even *if* the three references discussed above actually did treat CD, UC and pouchitis, there would be no reason to extrapolate that finding to ICAM-1 antisense treatments.

In addition, Applicants also note the Kono *et al.* is not available as prior art. The instant application has an actual filing date of Feb. 12, 2004. Kono issued May 4, 2004, after the actual filing date of the instant application, and has no earlier publication date. Therefore it is not art under 35 U.S.C. §§ 102(a) or (b). In addition, Kono is a national phase application of PCT/JP00/07855 which published in Japanese, not English. Therefore, Kono is not art under 35 U.S.C. § 102(e). *See M.P.E.P. §706.02(f)(1)II. Example 5* (stating that a national stage application of an international application not published in English has no §102(e) priority date).

Dr. Yacyshyn also rejects the Examiner's conclusion that one of skill in the art would have accepted that CD/UC treatments are interchangeable with pouchitis treatments because UC and pouchitis were closely interrelated as taught by Patel and Svaninger et al. *See Office Action* at page 8. Dr. Yacyshyn states that "[w]hile similarities between pouchitis and UC have led some to speculate that pouchitis may be a recurrence of UC, the generally accepted view was and continues to be that pouchitis is a disease of unknown origin distinct from UC." *Declaration* at ¶ 6 (citations omitted). In addition, Dr. Yacyshyn reviewed the Svaninger and Patel references relied on by the Examiner. He notes that Svaninger was published in 1993, and concludes that

"[t]he single statement speculating that pouchitis may be caused by a genetic component shared with UC patients is not sufficient to support the Examiner's conclusion in view of subsequent papers, including those referenced above, which have established that UC and pouchitis are most likely distinct diseases." *Id.* at ¶ 11.

Dr. Yacyshyn also reviewed the Patel reference, and concludes that "the observation in *Patel et al.* that serum ICAM-1 is elevated in active CD, UC and pouchitis is not sufficient to establish that the three diseases are closely interrelated." *Id.* at ¶ 12. Dr. Yacyshyn notes that ICAM-1 and related cell adhesion molecules are markers of inflammation generally, and therefore are elevated in a number of unrelated diseases, including chronic inflammatory liver disease, diabetes, some carcinomas, allograft rejection and systemic vasculitides. Thus, "the presence of elevated ICAM-1 in active UC and pouchitis does not establish that they are closely interrelated any more than it establishes that UC and diabetes are closely interrelated." *Id.* (emphasis added). Finally, he states that it is his expert opinion that the statement by *Patel et al.* that targeting ICAM-1 could, hypothetically, provide a new target for control of IBD is "nothing more than an untested hypothesis. Such an untested hypothesis was not sufficient to provide a reasonable expectation of success of treating pouchitis by inhibiting ICAM-1 expression to someone working in the field as argued by the Examiner." *Id.*

Finally, Dr. Yacyshyn addresses the Examiner's argument that one of skill in the art would have reasonably expected a successful pouchitis treatment (e.g. remission) based on studies of ISIS 2302 for treating CD. As noted above, Dr. Yacyshyn is the lead author of two of the main references relied on by the Examiner, and thus is eminently qualified to offer an opinion as to what the references he authored would have taught one of skill in the art. He states that it is his opinion that "the treatment of CD using intravenous administration of ISIS 2302 reported in *Bennett et al.* and *Yacyshyn et al.* (1999 and 2002) does not provide a reasonable expectation that an enema formulation of ISIS 2302 could treat pouchitis. ... treatment of CD by i.v. administration of ISIS 2302 was not viewed by those in the field as providing a reasonable expectation of successfully treating pouchitis by enema administration of ISIS 2302." *Id.* at ¶ 13 (emphasis added). He also notes that "[n]one of these references disclose the actual treatment of UC using ISIS 2302. And, even if they did, UC and pouchitis were recognized by experts in the field as distinct diseases, and there was no reasonable expectation in the field that treatments for

UC would successfully treat pouchitis..." *Id.* (emphasis added). Thus, the Examiner's statement that "it was also an art-recognized fact, at the time the invention was made, that ISIS 2302 is capable of producing a "durable remission" or "highly durable remission" in IBD patients..." (*Office Action* at page 9, emphasis added) is not supported by the evidence since the only IBD patients treated by ISIS 2302 where CD patients, and one of skill in the art would not have extended the results for CD to UC or pouchitis.

In conclusion, Dr. Yacyshyn states that:

> [I]t is my opinion that at the time of the invention, there was no reasonable expectation that an enema formulation of an antisense oligonucleotide having SEQ ID NO: 1 could successfully treat pouchitis. It is my opinion that, for the reasons discussed above, the references relied on by the Examiner, considered individually and in combination, do not support the conclusion that one of ordinary skill in the field would have had a reasonable expectation that the claimed methods would be successful. *Id.* at ¶ 14.

Based on the above, including the declaration of an expert in the field which is supported by numerous references, Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness because there was no reasonable expectation of success. For at least this reason, Applicants request that the Examiner withdraw the rejection of the pending claims as obvious in view of the cited references.

Unexpected Results

Even if the Office has established a *prima facie* case of obviousness, a point Applicants do not concede, Applicants submit that the claimed methods have unexpected results that are sufficient to demonstrate nonobviousness.

The results reported in Example 17 of the instant specification demonstrate that treatment with an enema formulation of antisense targeting ICAM-1 resulted in remission of 58% of patients. A month after treatment ended, 50% of the patients were still in remission. This is particularly surprising because the patients being treated were suffering from chronic, unremitting pouchitis that was unresponsive to conventional therapies. *See Specification* at ¶ [0320]. Thus, Applicants have provided a successful treatment for a chronic disease that currently has no conventional therapy available – a treatment which is successful in nearly two-thirds of the patients tested, and which maintains remission for at least a month after treatment

ceases. None of the cited references provide a basis for expecting such a successful outcome using an enema formulation of an antisense oligonucleotide to treat chronic, unremitting pouchitis.

The Examiner has asserted that the results of Example 17 "would have been reasonably expected at the time the invention was made in light of the ample evidence suggesting the ability of ISIS 2302 for producing durable remission in IBD patients and the clinical treatment effects (reduced/ceased inflammation) in chronic/active pouchitis patients treated with rectal/local administration of a therapeutic agent." *Office Action* at page 10 (emphasis added).

Dr. Yacyshyn, an expert in the field and author of the papers disclosing ISIS 2302 treatment of CD states that "the results reported in Example 17 of the specification are unexpected in view of what was known at the time of the invention, including the references relied on by the Examiner." *Declaration* at ¶ 15 (emphasis). Dr. Yacyshyn states that in view of the fact that none of the references relied on by the Examiner, including *Bennett et al.* and *Yacyshyn et al.* (1999 and 2002) report any data demonstrating the treatment of any IBD other than CD using ISIS 2302, "[i]t is therefore factually incorrect to state, based on these references, that at the time the invention was made it was an art-recognized fact that ISIS 2302 was capable of producing remission in any IBD patient other than a CD patient." *Id.* He restates that it is his expert opinion that "treatments for CD were not viewed as predictive of treatments for pouchitis. Therefore, the successful treatment of CD by i.v. administration of ISIS 2302 would not lead an expert in the field to expect that ISIS 2302 would successfully treat pouchitis as reported in Example 17." *Id.*

With respect to the "clinical treatment effects (reduced/ceased inflammation) in chronic/active pouchitis patients treated with rectal/local administration of a therapeutic agent" relied on by the Examiner, the data shown in the cited references for these therapeutic agents, none of which are known to be an ICAM-1 inhibitor, are not sufficient to establish a general expectation that an antisense oligonucleotide targeting ICAM-1 can successfully treat pouchitis. Indeed, none of these references suggest use of an ICAM-1 inhibitor to treat pouchitis. Dr. Yacyshyn states: "Nor does the treatment of pouchitis using tixocortol pivalate (*Karp, et al.*, Digest. Dis. and Sci., 33(3):85S-87S (1988)), ecabet sodium (*Kono et al.*), nicotine (*Sandborn 1998*) or xanthan gum enemas (*Sachetto*) provide any expectation of the results reported in

Example 17, as one of skill in the art would not expect the success of ICAM-1 antisense based on the success of compounds unrelated to ICAM-1 antisense." *Id.*

He concludes, stating that:

> It is particularly unexpected that the method described in Example 17 was able to achieve remission of 58% of patients at the end of treatment, and remission of 50% of the patients one month after treatment, since the patients were suffering from chronic, unremitting pouchitis that was unresponsive to conventional therapies. *Bennett et al.* report that 47% CD patients were in remission following treatment, and *Yacyshyn et al.* (2002) disclose that only 41% of CD patients experienced remission at the end of treatment, for a combined average remission rate of only 44%. As discussed above, it is my opinion treatments for CD are not interchangeable with treatments for pouchitis, and therefore these results are not directly comparable. In addition there are differences in the intensity of the disease, drug co-therapy, the amount and route of antisense administration, and length of treatment. However, comparing the results of Example 17 to those of *Bennett et al.* and *Yacyshyn et al.* (2002), the results of Example 17 are unexpectedly superior. *Declaration* at ¶ 16 (emphasis added).

Applicants remind the Office that unexpected results do not need to be recited in the claims. If the unexpected properties of a compound or method must always be recited in a claim, they would not be "secondary considerations" which can overcome a *prima facie* case of obviousness, but rather would always be limitations which are considered as part of the *prima facie* case. *See, e.g. M.P.E.P. §2145.* Rather, the unexpected results that flow from the claimed composition or method need only be unexpected in view of the closest cited reference. *See M.P.E.P. §716.02.*

In view of the fact that an expert in the field who was personally involved in the clinical trials the Examiner cites as the closest art views the results of the instant application as unexpected, Applicants submit that any *prima facie* case of obviousness is overcome. For this additional reason, Applicants request withdrawal of the rejection of the pending claims as obvious in view of the cited references.

35 U.S.C. § 112

Claims 44-45 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Specifically, claim 44 is rejected for having insufficient antecedent basis in claim 1 for the limitation "said reduction". Applicants respectfully disagree. Claim 1 recites "reduces the

occurrence". Accordingly, there is sufficient antecedent basis in claim 1 for the language in claim 44.

Claim 45 is rejected for having insufficient antecedent basis in claim 1 for the limitation "said patient". Applicants have amended claim 45 to recite "said human" to conform the language of claim 45 to the language of claim 1.

Double Patenting

Claims 1-2, 7-17, 25-42 and 44-45 are rejected under the doctrine of non-statutory obviousness-type double patenting over claims 9-11, 16 and 18 of US 6,096,722 in view of Sandborn '983, Patel and Yacyshyn 2002.

Claims 1-2, 7-17, 25-42 and 44-45 are rejected under the doctrine of non-statutory obviousness-type double patenting over claims 3, 6 and 9 of US 6,169,079 in view of Sandborn '983, Patel and Yacyshyn 2002.

Claims 1-2, 7-17, 25-42 and 44-45 are rejected under the doctrine of non-statutory obviousness-type double patenting over claims 1-10 of US 6,747,014 in view of Sandborn '983, Patel and Yacyshyn 2002.

Claims 1-2, 7-17, 25-42 and 44-45 are provisionally rejected under the doctrine of non-statutory obviousness-type double patenting over claims 86-93 of copending Application No. 11/237,063 in view of Sandborn '983, Patel and Yacyshyn 2002.

Claims 1-2, 7-17, 25-42 and 44-45 are provisionally rejected under the doctrine of nonstatutory obviousness-type double patenting over claims 54 and 59-63 of copending Application No. 11/720,745.

Applicants note that the secondary references cited in the double patenting rejections are a subset of those cited in the section 103(a) obviousness rejection discussed above. Applicants also note that the claims in copending Application No. 11/720,745 are directed to ulcerative colitis, not pouchitis. The cited claims of the patents and applications on which the double patenting rejections are based do not overcome the deficiencies in the Examiner's obviousness rejection identified above. Therefore, Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness in any of the above double patenting rejections for the same reasons discussed above with respect to the rejection under section 103(a). In addition, to the

extent that the Examiner has established a *prima facie* case of non-statutory obviousness, the results of the claimed method are unexpected in view of the cited claims and references as discussed above with respect to the section 103(a) obviousness rejection. Therefore, Applicants request withdrawal of the nonstatutory obviousness-type double patenting rejections.

Applicants also note that both the 11/237,063 and 11/720,745 applications were filed after the instant application. M.P.E.P. §804 provides in relevant part:

> If a "provisional" nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer. *M.P.E.P. §804(I)(B)(1).*

Consistent with M.P.E.P. §804, Applicants respectfully request that for this additional reason, the provisional double patenting rejections be withdrawn and the instant Application be allowed to issue.

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, Applicants are not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. Applicants reserve the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that Applicants have made any disclaimers or disavowals of any subject matter supported by the present application.

Patents and Applications

Applicants wish to draw the Examiner's attention to the following patents and/or applications. Applicants encourage the Examiner to review and monitor the prosecution of the

following patents and/or applications, including all Office Actions, throughout the pendency of this application.

Patent / Serial Number	Title	Issued / Filed
10/793,497	COMPOSITIONS AND METHODS FOR NON-PARENTAL DELIVERY OF OLIGONUCLEOTIDES	03.04.2004
6,747,014	COMPOSITIONS AND METHODS FOR NON-PARENTAL DELIVERY OF OLIGONUCLEOTIDES	06.08.2004
09/315,298	COMPOSITIONS AND METHODS FOR NON-PARENTAL DELIVERY OF OLIGONUCLEOTIDES	05.20.1999
11/237,063	COMPOSITIONS AND METHODS FOR NON-PARENTAL DELIVERY OF OLIGONUCLEOTIDES	09.28.2005
6,169,079	OLIGONUCLEOTIDE INHIBITION OF CELL ADHESION	01.02.2001
6,300,491	OLIGONUCLEOTIDE INHIBITION OF CELL ADHESION	10.09.2001
09/659,288	OLIGONUCLEOTIDE MODULATION OF CELL ADHESION	09.12.2000
6,093,811	OLIGONUCLEOTIDE MODULATION OF CELL ADHESION	07.25.2000
6,015,894	OLIGONUCLEOTIDE MODULATION OF CELL ADHESION	01.18.2000
5,843,738	OLIGONUCLEOTIDE MODULATION OF CELL ADHESION	12.01.1998
6,096,722	ANTISENSE MODULATION OF CELL ADHESION MOLECULE EXPRESSION AND TREATMENT OF CELL ADHESION MOLECULE-ASSOCIATED DISEASES	08.01.2000
6,111,094	ENHANCED ANTISENSE MODULATION OF ICAM-1	08.29.2000
10/454,663	OLIGONUCLEOTIDE MODULATION OF CELL ADHESION	06.04.2003
6,849,612	OLIGONUCLEOTIDE MODULATION OF CELL ADHESION	02.01.2005
6,887,906	COMPOSITIONS AND METHODS FOR THE DELIVERY OF OLIGONUCLEOTIDES VIA THE ALIMENTARY CANAL	05.03.2005
08/886,829	COMPOSITIONS AND METHODS FOR THE DELIVERY OF OLIGONUCLEOTIDES VIA THE ALIMENTARY CANAL	07.01.1997
07/939,855	OLIGONUCLEOTIDE MODULATION OF CELL ADHESION	09.02.1992
5,591,623	OLIGONUCLEOTIDE MODULATION OF CELL ADHESION	01.07.1997

5,514,788	OLIGONUCLEOTIDE MODULATION OF CELL ADHESION	05.07.1996
5,883,082	COMPOSITIONS AND METHODS FOR PREVENTING AND TREATING ALLOGRAFT REJECTION	03.16.1999
07/567,286	OLIGONUCLEOTIDE MODULATION OF CELL ADHESION	08.14.1990
10/559,401	OLIGONUCLEOTIDE MODULATION OF CELL ADHESION	N/A
09/659,288	OLIGONUCLEOTIDE MODULATION OF CELL ADHESION	09.12.2000
09/082,624	COMPOSITIONS AND METHODS FOR NON-PARENTAL DELIVERY OF OLIGONUCLEOTIDES	05.21.1998

CONCLUSION

Applicants submit that the present application is in condition for allowance and respectfully requests an action to that effect. If any issues remain, the Examiner is invited to contact Applicants' counsel at the number provided below in order to resolve such issues promptly. Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 8/17/11

By: 

Brenden S. Gingrich
Registration No. 60,295
Attorney of Record
Customer No. 55,389
(858) 707-4000

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